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GB 2057437 A US 4266517 A
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Scand.J.Rheumatol.,(1978), 7(1), p.55-60

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(54) The use of (+)-catechin in the treatment or prophylaxis of connective tissue disorders

(57) The present invention provides the use of (+)-catechin and derivatives thereof which will metabolise in vivo to yield (+)-catechin for the manufacture of a medicament for use in the treatment or prophylaxis of connective tissue disorders, eg. Marfan's Syndrome, arthritis.

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Medical Treatment

The present invention relates to the treatment of connective tissue disorders and in particular to a new medical use for (+)-catechin in the treatment of Marfan Syndrome and related diseases.

Marfan Syndrome is a condition characterised by reduced tensile strength of the connective tissues, particularly those supporting the ocular lens, the cardiac valves, the aorta and the skeletal system. The clinical manifestations of this disease are diverse; myopia, loose joints and chest deformity, for example, being commonly observed. Generally, however, the cardiovascular system is seriously affected, often resulting in severe degeneration and dilatation of the aortic wall and incompetence of the aortic valve. If left untreated, Marfan Syndrome is fatal in a large number of patients, primarily as a result of rupture or dissection of the aorta.

The loss of mechanical strength in the connective tissue is thought to be due to defective production of components of the connective tissue matrix, primarily of fibrillin and secondarily of elastin and collagen (see for example, Kainulainen et al., PNAS, 89: 5917-5921, 1992). Defective cross-linking of collagen has been demonstrated and breakdown of the fibres through the action of enzymes e.g. collagenase may be a contributory factor. Defects in the regulation of synthesis of connective tissue components such as collagen or elastin may also be involved although this has not been conclusively demonstrated.

At present there is no totally satisfactory treatment for Marfan Syndrome; frequent patient evaluation is needed, extended regimes of β-blockers are

often required and serious cardiovascular defects have to be treated by surgical repair. Similarly, other connective tissue disorders affecting the joints, such as arthritis, are treated primarily by alleviating the symptoms, by the use of analgesics and anti-inflammatory drugs, for example.

A need therefore exists for an improved method of treating Marfan Syndrome and other connective tissue disorders, and particularly for a treatment which acts at the level of the underlying condition, i.e. at the level of the defective matrix fibres and does not merely alleviate or reduce the symptoms once the condition has manifested itself.

I have now found that the known flavonoid (+)-catechin is of benefit in the treatment of connective tissue disorders. More particularly, we have found that (+)-catechin acts to render connective tissue and particularly collagen, and its related fibre elastin, more resistant in vivo to the effects of the enzymes collagenase, stromelysin, and elastase, which act to degrade the collagen, fibrillin and/or elastin fibres. Moreover, I believe that a similar defect may also be implicated in other connective tissue disorders such as arthritis. (+)-catechin may therefore be particularly useful in human and veterinary medicine for the treatment or prophylaxis of connective tissue disorders which are associated with collagen, fibrillin and/or elastin breakdown. In particular I propose the use of (+)-catechin in the treatment of Marfan Syndrome.

Furthermore, my studies have shown that a significant number of Marfan patients exhibit early osteo-arthritis suggesting that the deficiency responsible for the Marfan Syndrome may also be implicated in the pathogenesis of arthritis. I thus believe that (+)-catechin may also be of benefit in the treatment of arthritis.

In one aspect the present invention therefore provides the use of (+)-catechin and derivatives thereof which will metabolise in vivo to yield (+)-catechin for the manufacture of a medicament for use in the treatment or prophylaxis of connective tissue disorders, and particularly those associated with collagen, fibrillin and/or elastin breakdown.

In a further aspect the invention provides a method of treatment of the human or animal body to combat connective tissue disorders, and particularly with those associated with collagen, fibrillin and/or elastin breakdown, said method comprising administering an effective amount of (+)-catechin or a derivative thereof as defined above, to said body.

In another aspect the invention provides the use of (+)-Catechin for the treatment or prophylaxis of connective tissue disorders, and particularly with those associated with collagen, fibrillin and/or elastin breakdown.

(+)-Catechin (trans-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran, 3,5,7-triol) is a known compound described by Hardeggar et al, in Helv.Chim.Acta 40, 1819 (1957). It may be commercially obtained from ZYMA.S.A. of Nyon, Switzerland. Moreover (+)-catechin may be extracted from various plant species using conventional extraction techniques (Perkin and Yoshitake, J.Chem.Soc. 81, 116-69 (1902)).

GB-A-1341794 describes the use of (+)-catechin in the treatment of various hepatic disorders, but no mention of the therapeutic effects on connective tissue is made. The efficacy of (+)-catechin as a hepatic drug has been attributed to its activity firstly as a free radical scavenger and secondly in stimulating the immune system. These actions are not thought to be important and appear entirely unrelated to the effects of (+)-catechin on connective tissue.

It is preferable to employ (+)-catechin according to the present invention in the form of a pharmaceutical formulation.

The present invention therefore also provides a pharmaceutical composition for use in the treatment of connective tissue disorders, and particularly with those associated with collagen, fibrillin and/or elastin breakdown, said composition comprising (+)-catechin together with at least one pharmaceutically acceptable carrier or excipient.

Pharmaceutical compositions for use according to the present invention may be formulated in conventional manner, for example as described in GB-A-1341794. Thus the (+)-catechin may be incorporated, optionally together with other active substances, with one or more conventional carriers and/or diluents, e.g., with cornstarch, lactose, glucose, magnesium, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propyleneglycol, carboxymethylcellulose, or fatty substances such as hard fat or suitable mixtures thereof to produce conventional galenic preparations such as tablets, coated tablets, capsules, powders, suspensions, drops, ampoules, syrups or suppositories.

The precise dosage of the (+)-catechin to be administered and the length of the course of treatment will, of course, depend on a number of factors including, for example, the age and weight of the patient, the specific condition requiring treatment and its severity, and the route of administration. Generally, however, an effective daily dose is in the range of 1 to 3g, preferably 1.5g administered orally, parenterally or rectally 1 to 3 times, preferably 3 times a day.

The following non-limiting Example illustrates a pharmaceutical formulation suitable for use according to

the invention.

EXAMPLE 1

500mg tablet (diameter 10.5 mm) comprising 250mg (+)-catechin:

(+)-Catechin	250 mg
Wheat Starch	25 mg
Colloidal silicon dioxide	10 mg
Microcrystalline cellulose	100 mg
Lactose	105 mg
talc	10 mg
	500 mg

CLAIMS:

1. The use of (+)-catechin and derivatives thereof which will metabolise in vivo to yield (+)-catechin for the manufacture of a medicament for use in the treatment or prophylaxis of connective tissue disorders in humans or animals.

2. The use as claimed in claim 1 wherein said connective tissue disorder is associated with collagen, fibrillin and/or elastin breakdown.

3. The use as claimed in either claim 1 or claim 2 wherein said connective tissue disorder is Marfan Syndrome.

4. The use as claimed in claim 1 wherein said connective tissue disorder is arthritis.

5. The use as claimed in any one of claims 1 to 4 wherein said medicament is in a form suitable for administration orally, parenterally or rectally.

The Patent Office

Application No:	GB 9521725.3	**Examiner:**	Dr Carol Davies
Claims searched:	1-5	**Date of search:**	27 January 1997

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): A5B (BHA, BJA)

Int Cl (Ed.6): A61K

Other: ONLINE: CAS ONLINE; WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X	GB 2057437 A (CONTINENTAL PHARM) see whole document	1 at least
X	US 4268517 (CONTINENTAL PHARM) see whole document	1 at least
X	Scand. J. Rheumatol., (1983), 12(1), Rao, C. N. et al, pages 39-42. See abstract.	1 at least
X	Ital. J. Biochem., (1981), 30(1), Rao, C. N. et al, pages 54-62. See summary on page 61.	1 at least
X	Leather Sci. (Madras), (1979), 26(8), Rao, C. N. et al, pages 285-94. See abstract.	1 at least
X	Scand. J. Rheumatol., (1978), 7(1), Blumenkrantz, N. et al, pages 55-60. See abstract and last paragraph on page 60.	1 at least
X	Experientia (1976), 32(6), Francis, G. et al, pages 691-93. See summary on page 691.	1 at least

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.